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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/244,195	02/04/99	KITTO G	D6073

HM12/1017

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EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1648	2

DATE MAILED: 10/17/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/244,195	Kitto, G. And M. Burnett
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

X Responsive to communication(s) filed on *4 Feb 1999*.

_ This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

_ Claim(s) _____ is/are allowed.

X Claim(s) *1-10* is/are rejected.

_ Claim(s) _____ is/are objected to.

_ Claims _____ are subject to restriction or election requirement.

Application Papers

_ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

_ The drawing(s) filed on _____ is/are objected to by the Examiner.

_ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

_ The specification is objected to by the Examiner.

_ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

_ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

_ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

_ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

_ Interview Summary, PTO-413

_ Notice of Draftsperson's Patent Drawing Review, PTO-948

_ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Status of the Claims

1. Claims 1-10 are pending in the instant application.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims (1-5) are directed toward human immunodeficiency virus vaccines comprising recombinant plasmids encoding two proteins, one of which is required for surface exposure and the other which is derived from HIV. Methods of immunizing individuals in need of treatment with said vaccines are also claimed (claims 6-10). It was reported in the disclosure (pp. 1-2, bridging paragraph) that "The present invention relates to development of a live vaccine for human immunodeficiency virus (HIV)." The specification further states (p. 7, second paragraph) that "The present invention discloses development of a model live vaccine for HIV, using an attenuated strain of Salmonella engineered to surface express specific HIV proteins. In one embodiment, there is provided a live vaccine for human immunodeficiency virus comprising a recombinant plasmid containing

genes required for surface exposure and a gene encoding a human immunodeficiency virus protein." Thus, the focus of the invention as set forth in the specification, is to provide vaccines for the treatment or prevention of HIV infection.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: 1) The disclosure fails to provide adequate guidance pertaining to the nature and specificity of those immune responses (i.e., humoral or cell-mediated) that are capable of preventing or inhibiting HIV viral replication. Absent such a showing, the skilled artisan cannot ascertain which immunological parameters are indicative of protective or therapeutic immune responses. For instance, is an antibody response directed against a single HIV antigen sufficient to induce a protective or therapeutic response? What concentration of antibody in the vascular system will induce said responses? What type of immunization protocol will achieve these titers? Will a cytotoxic T lymphocyte directed against a specific HIV antigen result in a protective or therapeutic response? What is the titer of the CTL response that will provide an ameliorative response? What immunization regimen will induce the desired CTL response? Absent further guidance pertaining to these issues, the skilled

artisan has only been extended an undue invitation to further experimentation.

2) The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating protective or therapeutic immune responses to HIV. In order to achieve protection or disease abrogation, the skilled artisan needs to know which immunogens should be administered to any given subject. The skilled artisan would require a knowledge of the precise molecular determinants modulating these responses and the proper form (i.e., antigen packaged within a liposome, antigen expressed on the surface of a bacterial or viral carrier, antigen expressed from a DNA construct that is directly injected into the subject, or purified antigen in combination with a suitable adjuvant for direct administration) in which they should be administered. If the use of CTL epitopes is contemplated, the skilled artisan would require a knowledge of compatible MHC haplotypes before the vaccine could be administered. However, the specification is silent concerning all of these factors. Absent further guidance from applicants, the skilled artisan has only been extended another undue invitation to further experimentation to identify and characterize the immunogen of choice and determine the appropriate form and route of administration.

3) The disclosure fails to provide any guidance pertaining to the quasispecies nature of HIV-1 and -2. First, although HIV-1 and -2 are related, nevertheless, they display considerable genetic diversity (i.e., approximately only 38% genetic relatedness exists at the genomic level between HIV-1 and -2 isolates). Thus, the skilled artisan cannot conclude that an effective HIV-1 vaccine will also be effective against HIV-2, and vice versa, without a proper understanding of the factors discussed *supra* in the first two sections of the rejection. Second, even within any given family of HIV, extensive genetic diversity is present. For

instance, HIV-1 consists of a number of genotypically and phenotypically distinct clades (i.e., A, B, C, etc.). An effective immunogen against one clade may not be protective against a different clade, particularly if the molecular determinants modulating protective responses remain to be elucidated. Third, viruses evolve rapidly even within the same clade and patient. Many patients are initially infected with a genotypically and phenotypically distinct swarm, however, as infection proceeds a number of genotypically and phenotypically independent isolates emerge. Thus, a putative vaccine directed against an early isolate (i.e., T-cell tropic) may not be effective against a later isolate (i.e., macrophage tropic). Thus, considerable work remains to be done in this area.

4) The disclosure fails to provide any working embodiments demonstrating that a subject has been successfully protected from viral infection or that any given embodiment of the clinical sequelae associated with HIV infection has been ameliorated. Considering the unpredictability of the prior art, a working model would be required before the skilled artisan would reasonably expect the vaccines and immunization methods to function in the desired manner. It is noted that the specification describes the preparation of attenuated Salmonella strains (e.g., SL3261) that express lpp-ompA-RT or lpp-ompA-Tat fusion proteins. Mice were immunized with these strains and the immune responses elicited examined. However, this example does not constitute a proper working example due to the genotypic and phenotypic differences between humans and mice. Murine models do not enable the skilled artisan to make direct extrapolations pertaining to vaccine efficacy in humans.

5) The prior art (Haynes, 1993; Graham and Wright, 1995; Haynes, 1996; Lee, 1997) is unpredictable and teaches that HIV vaccine attempts have been unsuccessful to date due to a number of caveats

including the following: 1) A lack of understanding of the correlates of protective immunity. 2) A lack of understanding of those molecular determinants or antigens governing such responses. 3) The ability of HIV to spread via cell-cell mechanisms. 4) The ability of HIV to reside in immuno-privileged sites such as the CNS. 5) The quasispecies nature of HIV results in immune escape. 6) Inadequate animal models exist for HIV. All of these elements have contributed to vaccine failure. As Lee (1997) reflects on the status of phase I and II clinical vaccine trials he concludes (left col., p. 608) that "It is generally recognized that candidate HIV vaccines that have been tested in clinical trials do not elicit long-lasting antibodies or CTL responses."

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Correspondence

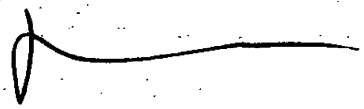
4. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

5. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

6. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be

reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,



Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

09 October, 2000

NOTES

- Serious vaccine enablement issues are present. Amendment of the claim language will not produce an allowance due to the large amount of art available on salmonella as a vaccine delivery vehicle.

- "The present invention relates to development of a live vaccine for human immunodeficiency virus (HIV)." (pp. ½, bridging para.)

- "The present invention discloses development of a model live vaccine for HIV, using an attenuated strain of Salmonella engineered to surface express specific HIV proteins. In one embodiment, there is provided a live vaccine for human immunodeficiency virus comprising a recombinant plasmid containing genes required for surface exposure and a gene encoding a human immunodeficiency virus protein." (p. 7, second para.)

- "In one embodiment of the present invention, there are provided recombinant plasmids, containing the Lpp-OmpA genes required for surface exposure, followed by the genes for the HIV-1 proteins, Reverse Transcriptase, or Transactivating protein (Tat). In a preferred embodiment, the plasmids are electroporated into an attenuated strain of Salmonella, SL3261." (p. 7, third para.)

DATA

- Used attenuated Salmonella SL3261; fusion protein comprising E. coli lipoprotein signal sequence (lpp) (aa 1-9) linked to the E. coli outer membrane protein ompA (aa 46-159)

- Made lpp-ompA-Tat (HIV-1) and lpp-ompA-RT (HIV-1)??? fusions

- Electroporate said constructs into Salmonella SL3261

- Immunized Balb/C mice with attenuated Salmonella

- IgA response observed in mice; splenocyte proliferative responses to immunizing Ag also observed;